Application/Control No.: 10/693042
Art Unit: 1647

REMARKS

Claims 1-28 remain pending in the application. Claims 1-4, 8-11, 15-18 and 22-25 have been amended herein. No new matter has been introduced by any of the amendments.

The time taken by Examiners Wegert and O'Hara to participate in a telephone discussion with Dr. Richard Sterner on September 12, 2007 is acknowledged with gratitude. The Examiners' input and attention are much appreciated. The amendments herein to the claims and the remarks below are reflective of the issues discussed.

The remarks below not only reiterate the points made/discussed during the September 12, 2007 telephone conference but provide additional details. The remarks immediately following provide key background and insight into the principles of the present invention. The specific rejections will then be addressed in light of this information and what was discussed on September 12th.

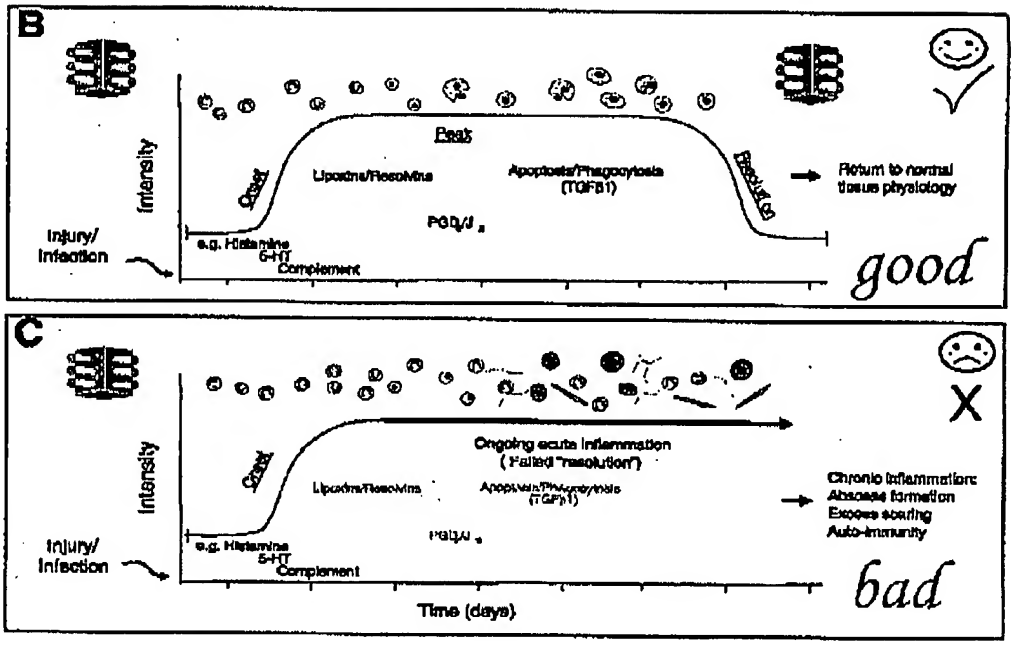
"Good" *vs* "Bad" Inflammation and the Onset *vs* Progression of Chronic Inflammation

In response to injury or infection, specialized activated leukocytes migrate to the damaged/infected sites to neutralize and eliminate potentially injurious/toxic stimuli. This inflammatory response protects the body and plays a critical role in the recovery to normal tissue physiology, e.g., wound repair following injury. The inflammatory response is well regulated and it is resolved within 6-7 days after the insult (Fig. B below). However, in instances when it is dysregulated it persists and becomes chronic inflammation having deleterious consequences

with pathologic outcome, e.g., autoimmune diseases, or tissue decay instead of wound repair following injury (Fig. C below).

These figures were taken from the review by Serhan et al, *The FASEB Journal* (2007) 21:325-332, a copy of which is enclosed and which is listed on the attached Form PTO/SB/08b.

Fig. B illustrates the "Good" normal course of inflammation. Fig. C illustrates the "Bad," a course in which inflammation is dysregulated, becoming chronic and leading to pathology.



The review by Serhan et al, *The FASEB Journal* (2007) 21:325-332 (enclosed) examines the current knowledge as to how inflammation is regulated and resolved. It provides an overview of some key points at which inflammation could be manipulated to prevent, for example, the switch into chronic inflammation. It emphasizes the significance of temporal progression of events, that, for example, early intervention within the "good" phase could be deleterious instead of curative. It also notes that in the autoimmune diseases, the persistence of the inflammatory response appears to become divorced from the inciting agent.

The preceding introduction provides background to the principles of this invention and explanation to the remarks below.

Treating chronic inflammation in spinal cord injury with β-interferon

This invention relates to the pathologic processes taking place at the histologic level following spinal cord injury. It identifies the type of pathologic process: chronic inflammation

and the timing of its onset following injury; it describes when and how it can be manipulated, stopped or down-regulated once it starts using a well-characterized drug, β-interferon, which is used to intervene with chronic inflammation in the autoimmune neurodegenerative disease multiple sclerosis (MS). The invention is intended to adapt an already established clinical procedure for the treatment of MS — the use of beta interferon — to treat human spinal cord injury.

The basis for the invention is the unexpected discovery that the underlying/crucial event leading to the pathologic hallmarks of spinal cord injury and MS are identical; in both it is the breakdown of the blood brain/cord barrier (BBB). The primary cause of MS, the autoimmune trigger, is unknown; however, the persistent inflammation is due to the BBB breakdown [De Vries et al. (1997) *Pharmacol Rev* 49:143-155; Pachter et al. (2003) *J Neuropathol Exp Neurol.* 62:593-604]. Once the BBB is broken, both in spinal cord injury and in MS, chronic inflammation ensues, resulting in tissue degenerative processes, such as demyelination. It was demonstrated in clinical trials in MS patients and in an animal MS model that chronic inflammation can be contained/prevented by treatment with beta interferon.

The focus of the invention is chronic inflammation which leads to the pathology in spinal cord injury, the tissue decay. This invention is targeted to halt [intervene with] the onset or to halt/attenuate the progression of chronic inflammation in spinal cord injury with β-interferon. It is already established both in human and animal model that β-interferon can attenuate/diminish the chronic inflammation expressed in MS as progressive demyelination.

Below, the specific rejections leveled in the Office Action are addressed in the wake of the September 12th discussion and the information provided above.

The issue raised with respect to claims 4, 11, 18 and 25 and the trade names Betaseron and Avonex recited therein was discussed. The Examiners agreed, upon further reflection, that this was not really an issue and indicated to Dr. Sterner that the rejection would be withdrawn.

The phrase "or later" cannot be considered indefinite in the context of the present invention

The indefiniteness rejection of claims 6, 7, 13, 14, 20 and 21 for reciting the phrase "or later" was discussed. It was explained to the Examiners why this phrase cannot be considered

indefinite in the context of the present invention and how it would be perfectly well appreciated by one of skill in the art reading the present application. Paragraphs 16 and 35 of the application as filed were particularly referenced by Dr. Sterner. These arguments are further expanded below.

Data from our studies suggest that in the early phase after spinal cord injury normal tissue repair processes take place, including the down-regulation of inflammation as seen in Fig. B above from the review of Serhan *et al*. The data indicate that the switch from tissue repair to decay occurs during days 10-14 after injury. Further using the molecular marker for onset of chronic inflammation at the BBB, VCAM-1 (vascular cell adhesion molecule-1), it was determined that in the spinal cord the chronic inflammation is triggered at about day 11 after injury.

There are two waves of onset of chronic inflammation. The first wave is triggered at the lesion site proper, at the primary impact area at about day 11 postinjury. This is the first wave which leads to a massive tissue decay at the lesion site.

There is a secondary onset of chronic inflammation which is triggered in the intact tissue at the margin of the lesion site; this is a secondary (ripple wave) which penetrates and spreads into the intact undamaged cord tissue. This secondary onset of chronic inflammation within the intact normal tissue occurs at about the 4th week postinjury. This secondary wave leads to a secondary tissue decay, for the most part to robust demyelination. It persists and constantly penetrates into the intact undamaged spared tissue. This is an everlasting decay process.

If one treats with beta-interferon starting at day 11 postinjury, the onset of chronic inflammation is halted; the primary wave is stopped and obviously there is no secondary wave. However, if one misses the primary timing, the secondary timing for halting the penetration of chronic inflammation into the spared tissue would be at the 4th week postinjury. It is important to understand that whether one begins treatment as early as the 11th day or waits until the 4th week or later, one is treating the same problem, namely, chronic inflammation. However, the later the treatment starts postinjury, the less the capacity of beta interferon is to intervene and effectively suppress the chronic inflammation.

The assumptions/arguments above are supported by the effectiveness of beta interferon in significantly reducing the number of relapses and slowing the progression of the disease and in

suppressing the chronic inflammation in MS. The treatment is most effective for the Relapsing-Remitting MS; however, it is started at different time points after the first relapse.

Claims 1-28 are enabled for both "11th day or later" and "4th week or later"

The rejection of claims 1-28 as not being enabled for "11th day or later" and "4th week or later" was discussed. This rejection in closely related to the rejection addressed immediately above, and the same arguments and comments that were presented above are effective in demonstrating that claims 1-28 are indeed enabled for "11th day or later" and "4th week or later."

VCAM-1 is only a molecular marker for the onset of chronic inflammation

Further in connection with the enablement issue, the Examiner's remarks on VCAM-1 on pp. 4 and 5 of the Office Action were discussed. VCAM-1 is an endothelial cell adhesion protein and its role in the onset of chronic inflammation in central neural tissues is very well defined. It was explained that it is not important what attends VCAM-1 rise, that VCAM-1 is just a marker used to determine/monitor the onset of chronic inflammation and that once VCAM-1 is upregulated, its levels remain very high and it never goes away. Also, VCAM-1 helped determine that the onset of chronic inflammation is related to the pathology of the BBB at the lesion site as is the case in MS. Paragraph 33 of the application was referred to during the discussion as explaining the basis for the invention with the further clarification, however, that this disclosure is not meant to implicate the VCAM-1 pathway as integral to the invention. Also cited in this part of the discussion were paragraphs 8, 13 and 16 of the application.

Other remarks

Also discussed in connection with the enablement rejection were the Examiner's statements: "Since applicants did not administer β-interferon to the animals after injury, ..." and "it is not known if the secondary inflammatory process, once begun, is reversible." In the context of the background and arguments presented during the telephone conference and further

discussed above, it can be seen that these statements/comments are irrelevant/inappropriate to the analysis at hand.

Further in connection with the enablement rejection, the issue of "prevention" recited in claim 8 was discussed. The Examiners explained that this term is regarded as objectionable, as it conveys that absolutely none of the unwanted effects are manifested. In response, the term "prevention" in claim 8 has been replaced by "halting," to convey halting the onset or halting the progression of chronic inflammation.

Finally, the rejection of claims 1-3, 8-10, 15-17 and 22-24 as not meeting the written description requirement was discussed. The Examiners indicated their belief that the disclosure only of Betaseron and Avonex as specific examples was insufficient to meet the requirement with respect to what is meant by the term "analogue". When queried as to what would be a sufficient number of examples, the Examiner indicated that three was a "fair number."

The chemical definition of an analogue of a compound is one that has a similar structure, differing only slightly in composition. In the present context and in the context of U.S. patent practice in general, it would be clearly understood that the phrase "analogue thereof" refers not only to a compound with a similar structure but one with similar biological activity. Nonetheless, in the interest of absolute clarity, claims 1-3, 8-10, 15-17 and 22-24 have been amended to recite that β-interferon analogue is a biosimilar analogue, a term universally understood by those in the field to indicate an analogue with similar biological activity.

Currently there are four commercially available examples meeting these criteria: Betaseron, Avonex, Rebif and Cinnovex. Accordingly, the Examiners' stated criterion for fulfilling the written description requirement has been met, and this rejection should be withdrawn. In conjunction with this demonstration that the requirement has been met, claims 4, 11, 18 and 25 have been amended to add Rebif and Cinnovex to the Betaseron and Avonex recited in the original claims.

Several paragraphs from the patent application as originally filed that are relevant to the foregoing remarks, some referred to particularly during the September 12th discussion, are set forth below for the Examiner's convenience and are denoted by paragraph number:

"[0033] This invention is intended to treat chronic human spinal cord injury. The invention is intended to adapt an already established clinical procedure for the treatment of the neurodegenerative disease multiple sclerosis (MS) -- the use of beta interferon — to treat chronic human spinal cord injury. The basis for the invention is the unexpected (counterintuitive) discovery that the underlying/crucial event leading to the pathologic hallmarks of spinal cord injury and MS are identical; in both it is the breakdown of the BBB. The primary cause of MS, the autoimmune trigger, is unknown; however, the BBB breakdown is a consequence of the autoimmune response to the self central neural components [De Vries et al. (1997) *Pharmacol Rev* 49:143-155; Pachter et al. (2003) *J Neuropathol Exp Neurol.* 62:593-604] In SCI the BBB breakdown is due to the injury to the spinal cord blood vessels. Once the BBB is broken, both in SCI and in MS, chronic inflammation ensues resulting in tissue degenerative processes, such as demyelination. As discussed above, it was demonstrated in clinical trials in MS patients and in an animal MS model that chronic inflammation can be contained/prevented by treatment with beta interferon, suggesting a direct effect on VCAM-1 levels (reduction). Since the underlying event leading to chronic inflammation in chronic SCI has now been found to be identical to the event in MS, the present invention is directed to beta-interferon treatment to prevent chronic inflammation and its devastating consequences in chronic SCI.

[008] The working hypothesis that led to this invention is that the breakdown of the blood-cord barrier following SCI leads to chronic inflammation which is the culprit in SCI pathology. ... It is assumed that the loss of function in the intact/spared fibers is due to the secondary damage caused by the chronic inflammation which is triggered at about the 3rd week after spinal cord injury.

[0016] Our preliminary data, in a rat spinal cord contusion injury model, show that chronic inflammation at the lesion site is triggered, at the molecular level, only by the end of the 2nd and/or 3rd week after injury. Our data show that following injury the expression of VCAM-1 on cord endothelial cells starts to increase above background levels only by the end of the 2nd week and/or 3rd week and that it becomes expansive throughout the lesion site by the 4th week postinjury [Burrows, et al., (2002) Program No. 133.10., *2002 Abstract Viewer/Itinerary*

Planner. Washington, DC: Society for Neuroscience, Online]. Based on our observations, it is anticipated that beta interferon would suppress the pathologic enhanced expression of VCAM-1 following spinal cord injury in the same manner it does in experimental models of MS. It is anticipated that beta interferon would gain access to the lesion site via the leaky BBB and would exert its physiological function, inhibiting thereby the chronic inflammation and demyelination and thus leading to rescue of neurologic function of the spared, uninjured spinal cord tissue including the spared brain-cord fiber tracts.

[0035] The analysis suggests chronic inflammation associated with SCI is an ongoing process at the site of lesion that can be stopped/attenuated by treatment with beta interferon. Preferably, the treatment should start at about the 11th day after injury when the decay is triggered, but it can be applied months or even years after injury to rescue the spared tissue from further degeneration.

[0042] ... Altogether, it appears that the switch from repair to decay occurs during day 10-14 after injury.

[0013] VCAM-1 on blood-brain barrier endothelium is one of the major mediators of leukocyte migration through the barrier during inflammation [Engelhardt et al. (1994) *J Neuroimmunol.* **51**:199-208; De Vries et al. (1997) *Pharmacol Rev* **49**:143-155; Risau et al. (1998) *Patol Biol.* (Paris) **46**:171-175]. Recent data in an experimental animal, in a rat MS model, suggest that beta interferon directly modulates inflammatory events at the level of cerebral endothelium [Floris et al., *J. Neuroimmun.* (2002) **127**: 69-79]. It was demonstrated in that study that beta interferon treatment resulted in a marked reduction of perivascular infiltrates; this was coupled to a major decrease in the expression of the adhesion molecules ICAM-1 and VCAM-1 in brain capillaries. Further, monocyte adhesion and subsequent migration were found to be predominantly regulated by VCAM-1. These data indicate that beta interferon exerts direct anti-inflammatory effects on brain endothelial cells, thereby contributing to reduced lesion formation as observed in MS patients."

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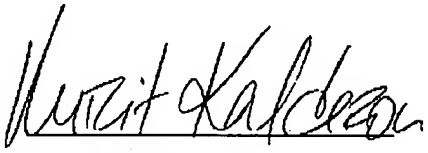
Conclusion

The amendments to the claims and remarks herein are responsive to the suggestions made by the Examiners during the September 12, 2007 telephone conference and are reflective of the issues discussed and understanding reached at that time. All outstanding issues have been addressed, and the application is in condition for allowance. Reconsideration and allowance of the application with pending claims 1-28 as presented herein are respectfully requested.

No additional fees should be due in connection with this communication. However, should it be determined that an additional fee is due for any reason, the Commissioner is hereby authorized to charge it to the credit card designated in the accompanying Form PTO-2038.

Dated: October 22, 2007

Respectfully submitted,



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Enclosures:
Form PTO/SB/08b
Review by Serhan et al., *The FASEB Journal* (2007) 21:325-332.
Form PTO-2038